Oxytocinergic regulation of cardiovascular function: studies in oxytocin-deficient mice

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In recent studies, we showed that endogenous OT acts as a neuromodulator in a brain stem region critical in cardiovascular coordination, the nucleus of the solitary tract-dorsal vagal complex (NTS/DVC) (5, 16, 27). Combining measurement of brain stem peptides with functional responses following local OT receptor blockade, we showed that activation of oxytocinergic projections is important in the heart rate (HR) response to exercise. OT appeared to mediate the smaller tachycardic response to exercise, characteristic of trained animals (5, 16, 27). Baroreflex gain was also affected by central OT administration, an increase after NTS/DVC injection (16), and a decrease after intracisternal injection (32). Autoradiographic binding and immunohistochemical staining methods verified the presence of the peptide and its receptor in key brain stem centers (6, 24, 26, 30, 40).

The study of peptidergic modulation of cardiovascular function has largely depended on the use of exogenous receptor agonists and antagonists. These experiments require injections into specific brain regions to localize effects as well as long-term maintenance of pharmacological blockade. The development of new animal models in which genes are removed or added allows for investigation at a different level. The OT knockout mouse strain (OTKO), developed by Young et al. (46), lacks the ability to synthesize OT. This genetic strain shows a deficit in milk ejection, changes in social behavior, and enhancement of sodium consumption (1, 10, 34, 46, 47). However, there is a lack of information on the cardiovascular changes associated with this genetic modification. We developed sophisticated methods for the conduct of cardiovascular studies in mice, allowing for chronic, long-term measurements of blood pressure (BP) and HR (2, 23). Studies were designed to compare OTKO −/− with its control +/+ group in terms of 1) baseline BP and HR, 2) baroreceptor reflex control of HR, 3) sympathetic and parasympathetic tone to the heart, and 4) sympathetic tone to the periphery.


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METHODS

Animals. Male wild-type (OT +/-, control) and OTKO --/-- mice (~30 g) were obtained from a colony at the University of Pittsburgh. The founders were derived from the strain developed by Dr. W. S. Young III and colleagues (Bethesda, MD) (46). Genotypes were determined from DNA extracted from tail using a polymerase chain reaction technique. The experimental mice (+/+ and --/--) were produced by breeding heterozygote (+/-) parents. Although this breeding strategy is time and labor intensive, it produces animals with similar genetic and environmental backgrounds. Animals were housed in clear cylindrical cages (Instech Laboratories, Plymouth Meeting, PA) at 22°C, under a 12:12-h light-dark cycle (0500–1700 lights on), and with ad libitum access to water and standard mouse chow. The Laboratory Animal Care and Use Committee of Wright State University approved all experimental protocols.

Animal surgery. Animals were prepared with chronic carotid arterial catheters according to the method of Li et al. (23). The catheters were formed from Micro-Renathane tubing (0.025-mm OD × 0.012-mm ID) with the end heat-stretched (about one-half the original diameter) and beveled. Mice were anesthetized with a ketamine-xylazine mixture (70:6 mg/kg im) and the catheter was inserted into the carotid artery. The external extremity of the catheter was tunneled subcutaneously to pass through a polysulfone button (model LW62; Instech Labs), surgically attached to the back muscles. The catheter was covered with a stainless steel spring, which was attached to a fluid swivel (model 375/25; Instech Labs) mounted on top of the cage. The tether and swivel system allowed the animal to move freely, while protecting the arterial catheter. The catheter was connected to a flow-through pressure transducer (model 041-500503A; Argon, Athens, TX), which was continuously infused with heparinized saline (80 U/ml, 20 µl/h syringe pump, model 220; Kd Scientific, Boston, MA). The heparinized saline infusion was required to maintain catheter patency. The animals were allowed to recover from surgery for a minimum of 3–5 days before experimentation.

Experimental protocols. The first experiment determined baseline levels of BP and HR using continuous cardiovascular measurements (3–5 days). The continuous recording method is preferable because it provides a true nonstress baseline without the complications of animal handling.

The second experiment evaluated baroreceptor reflex control of HR, determined by HR responses to pressor and depressor agents. Baroreceptor activation was produced by bolus intra-arterial injections (5–30 µl) of phenylephrine (20 µg/ml) and sodium nitroprusside (50 µg/ml). The catheter was loaded with the drug solution and the injections were made from low to high volume (5–30 µl) with a saline flush (20–30 µl) at the end of the injection series. This method avoids the complications of volume overload with repeated flushing. Subsequent injections were not made until the cardiovascular parameters had returned to preinjection levels. BP and HR measurements were made during the baseline period (immediately before injection) and during the development of the pressor or depressor responses.

The third experiment determined vagal and sympathetic tone, using blockade of β2- and cholinergic receptors. OTKO --/-- and control +/- mice were given atropine (30 µl, 2 mg/kg) or atenolol (50 µl, 4 mg/kg) via the arterial catheter. The drugs were given in a counterbalanced design, atropine (maximal tachycardia) followed by atenolol (maximal bradycardia) and the opposite order for the second test (1–3 days later). Sequences were randomized between mice, and basal and double blockade values were averaged for the two injection sequences. Preliminary tests using acetylcholine and isoproterenol were performed to verify the efficacy of the antagonist treatment. Ganglionic blockade was tested using hexamethonium (10 µl, 6 mg/kg). BP measurements after ganglionic blockade were made at the nadir of the pressor response (20–30 s after injection). These measurements were made at the end of the experiment (up to 2 wk after cannulation) and the pulse pressure was lower. For this reason, only the BP data are provided.

Data collection. The calibrated pressure transducer was connected to a computerized data-acquisition system (model MP100WSW; BIOPAC Systems, Santa Barbara, CA), specifically designed for cardiovascular measurements. BP was sampled at different rates for the acute and chronic studies (500 and 100 Hz, respectively). The lower sampling rate was used for continuous measurements because of the data-storage requirements. Data were recorded online using a computer (XPS-D300; Dell Computer, Austin, TX) and a removable disk storage system (Jazz Drive; Iomega, Roy, UT). Data were processed beat to beat. Mean arterial pressure (MAP) was calculated using the formula MAP = diastolic BP (DBP) + systolic BP (SBP) − DBP/3 and the instantaneous HR by the period between SBP in two consecutive beats.

To obtain data on baseline MAP and HR, cardiovascular data from a 3- to 5-day period were compiled to provide mean levels. For determination of reflex control and vagal and sympathetic tone, maximal changes of MAP and HR relative to previous control values were calculated. Baroreceptor reflex control of HR was estimated using the sigmoid logistic equation (22) fitted to the data points. The equation correlates absolute HR and MAP values during transient pressure changes induced by phenylephrine or sodium nitroprusside injections

\[
HR = P_1 + \frac{P_2}{1 + e^{P_3(MAP - P_4)}}
\]

where \(P_1\) is the lower HR plateau, \(P_2\) is the HR range, \(P_3\) is a curvature coefficient that is independent of range, and \(P_4\) is the MAP at one-half the HR range, i.e., \(MAP_{50}\). The maximum gain (G) is given by the formula \(G = -P_2 \times P_3/4\) and the upper plateau = \(P_1 + HR\ range/2\). The maximal tachycardic (upper plateau − average HR) and bradycardic responses (average HR – lower plateau) and the MAP range (corresponding to the interval in the x-axis between lower and upper plateau) were also calculated (16). Parameters of the sigmoid fitting were used to compare the OTKO --/– and control +/- groups.

Statistical analysis. Values are reported as means ± SE. Differences between groups were compared by Student’s t-test (baseline values and parameters of logistic curve) or two-way ANOVA (groups and pre/posttreatment values), as appropriate. Two-way ANOVA for repeated measurements was used to compare serial injections of phenylephrine and sodium nitroprusside between groups. Significance level was set at \(P < 0.05\).

RESULTS

BP and HR. OTKO --/– mice demonstrated a mild hypotension with no change in HR (Fig. 1). Twenty-four-hour mean MAP was ~7% lower in OTKO --/– mice compared with control +/- mice (102 ± 3 vs. 110 ± 3 mmHg, \(P < 0.05\)). Baseline HR was not different between the groups (507 ± 18 vs. 523 ± 27 beats/min, control +/- vs. OTKO --/– group).
Vagal and sympathetic tone. Intra-arterial injections of atropine or atenolol did not change MAP in either group (Table 1). Cholinergic blockade caused a marked increase in HR in OTKO –/– animals, with no significant changes observed in control +/- mice (+77 ± 25 vs. +5 ± 15 beats/min, OTKO –/– vs. control +/- mice). The HR response to sympathetic blockade was not significantly different between the groups (−62 ± 21 vs. −124 ± 25 beats/min, OTKO –/– vs. control +/- group). Intrinsic HR, determined as the level achieved after double adrenergic and cholinergic blockade (Fig. 2A), was significantly higher in OTKO –/– than in control +/- mice (483 ± 12 vs. 413 ± 22 beats/min, OTKO –/– vs. control +/- group). Intrinsic HR values and maximal HR changes observed following cholinergic or adrenergic blockade are used for the calculation of sympathetic and vagal drive to the heart. As shown in Fig. 2A, sympathetic tone was high and of similar magnitude in both groups (+146 ± 16 and +157 ± 15 beats/min over respective intrinsic HR). Vagal tone was not significantly different between the groups (−51 ± 20 vs. −12 ± 18 beats/min below intrin-

Table 1. Baseline values of MAP and HR before and after treatment with atropine, atenolol, and Hex in control +/- and OTKO –/– mice

<table>
<thead>
<tr>
<th></th>
<th>Control +/-</th>
<th>Atropine</th>
<th>Atenolol</th>
<th>Hex</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>113 ± 5</td>
<td>113 ± 5</td>
<td>113 ± 5</td>
<td>113 ± 5</td>
</tr>
<tr>
<td>Change</td>
<td>(0 ± 4)</td>
<td>(0 ± 4)</td>
<td>(0 ± 4)</td>
<td>(0 ± 5)</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>−559 ± 25</td>
<td>564 ± 25</td>
<td>526 ± 28</td>
<td>401 ± 21</td>
</tr>
<tr>
<td>Change</td>
<td>(+5 ± 15)</td>
<td>(+5 ± 15)</td>
<td>(+5 ± 15)</td>
<td>(+124 ± 25)</td>
</tr>
<tr>
<td>OTKO –/–</td>
<td>103 ± 6</td>
<td>102 ± 7</td>
<td>101 ± 5</td>
<td>106 ± 5</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>553 ± 25</td>
<td>630 ± 23 *</td>
<td>495 ± 23</td>
<td>433 ± 26 *</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 9 control +/- and oxytocin knockout (OTKO) –/– mice for atropine/atenolol; n = 5 control +/- mice and n = 6 OTKO –/– mice for hexamethonium (Hex). Numbers in parentheses are the responses to atropine, atenolol, or Hex. Blood pressure and heart rate (HR) data are presented for the Hex group. *P < 0.05 vs. baseline; †P < 0.05 vs. control. MAP, mean arterial pressure.
sic HR; Fig. 2A). Although the groups showed a similar HR range, sympathetic drive, and baseline HR (indicated by arrows in Fig. 2A), the OTKO −/− mice operated at a lower level of sympathetic activity. The net result is that these mice have a higher sympathetic reserve to be manipulated during depressor challenges (Fig. 2B).

**Ganglionic blockade.** To quantify sympathetic drive to the periphery, we used ganglionic blockade with hexamethonium (Table 1). Hexamethonium produced similar MAP reductions in the control +/+ and OTKO −/− groups (decrease of ~15 mmHg). This suggests that the sympathetic drive to the vessels is not altered in the knockout mice.

**Baroreflex function.** Bolus injections of phenylephrine and sodium nitroprusside were used to test baroreceptor reflex control of HR. Graded doses of phenylephrine (3–26 μg/kg) increased MAP from 13 ± 2 to 40 ± 5 mmHg, whereas sodium nitroprusside (8–50 μg/kg) decreased MAP by 14 ± 2 to 39 ± 5 mmHg. This is a sufficient range of pressures to test baroreflex function. There were no differences in the pressor or depressor responses between the groups (Fig. 3). Sigmoidal curves were fitted to HR and MAP data obtained during the pressor/depressor challenges. Examples of individual curves in OTKO −/− and control +/+ mice are shown in Fig. 4. The average sigmoidal curves and calculated parameters for both groups are presented in Fig. 5 and Table 2, respectively. Baroreflex function differed between OTKO −/− and control +/+ mice. There was a sharp increase in the reflex gain in the OTKO −/− group (~13.1 ± 2.5 vs. −4.1 ± 1.2 beats·min⁻¹·mmHg⁻¹) with a significant decrease in the pressure interval required to change from maximal tachycardia to maximal bradycardia (93 ± 12 vs. 40 ± 3 mmHg, control +/+ vs. OTKO −/− mice, a reduction of 57%). These changes were accompanied by a nonsignificant change in the functional range of the HR response (151 ± 33 vs. 203 ± 22 beats/min, control +/+ vs. OTKO −/− group) (Table 2 and Fig. 5). However, the OTKO −/− group showed a significant reduction in control HR values maintained during baroreflex testing (577 ± 12 vs. 511 ± 17 beats/min, control +/+ vs. OTKO −/− group; Table 2), with no change in MAP. The smaller average HR in a similar reflex HR range explains why the OTKO −/− group shows a difference in maximal bradycardia (~51 ± 9 vs. −102 ± 21 beats/min, OTKO −/− vs. control +/+ group, P < 0.05; Fig. 6) and a potentiation of reflex tachycardia (+152 ± 20 vs. +49 ± 14 beats/min, OTKO −/− vs. control +/+ mice, P < 0.05; Fig. 6). Facilitation of the tachycardia response in OTKO −/− mice is in accordance with the higher sympathetic reserve observed in this group (Fig. 2).

**DISCUSSION**

With the use of the OT-deficient model, we uncovered important new findings on OT's role in BP and baroreflex/autonomic balance. The data provide the first experimental evidence for a role of endogenous OT in the maintenance of tonic BP, because OTKO −/− mice showed a small but consistent hypotension. Alterations in baroreflex function were noted in mice lacking OT, seen as an increase in the gain of the baroreflex curve and an alteration in the operating pressure range. Finally, there was a change in autonomic balance to the heart with a greater response to cholinergic blockade and an indication of higher sympathetic reserve.

There is much evidence to show that brain peptides regulate BP and autonomic balance. For the highly complementary peptides vasopressin and OT, there are effects on BP, HR, and baroreflex activity (11, 31–33, 36, 44). There are differences, which are dependent on the route of administration (central or peripheral), the time frame (short or long term), and the animal species. For example, intracisternal OT injection produced no change in BP or HR, but it altered baroreflex sensitivity (32, 33). Injection of OT into the rostral brain stem produced a rise in BP and HR as did peripheral administration (26, 31, 33). To further investigate the impact of the peptides, investigators tested the effect of peptide antagonists, antisense oligonucleotides, and specific brain lesions on physiological function. We reported that both neurotoxin brain lesions and centrally injected OT antisense oligonucleotides attenuated the tachycardic responses to stress (8, 29). A specific OT antagonist altered exercise tachycardia as...
well as baroreflex function (5, 16). The antagonist actions were opposite to the peptide’s effects, suggesting a specificity of the response.

As an extension of these pharmacological studies, we proceeded to use the OT gene deletion model (46). The objective was to examine cardiovascular regulation in the absence of the peptide, with the rationale that the physiological findings would provide information on function. The advantage of the knockout model is that the compound of interest, in this case OT, is absent from all tissues at all times, from uterine development to adulthood. Studies are not dependent on the efficacy of drugs or on changing plasma/tissue levels. However, the genetic model, at the same time, raises questions related to possible developmental and/or compensatory effects of the peptide removal.

Initial studies asked the question as to whether basal BP and HR are altered in OTKO +/− mice. Methods established in the laboratory allow for the long-term measurement of cardiovascular parameters in conscious, unstressed mice (2, 23). This is critical for the measurement of basal levels since handling, noise, or other environmental stimuli can affect BP and HR. Results demonstrated a small, but consistent, hypotension in OT-deficient mice, supporting a role for OT in BP maintenance. This effect was observed only in the chronic monitoring study and not in the acute paradigms. This demonstrates the requirement for continual measurements (extensive data pool) to reveal small pressure differences (a 7% reduction). The results were verified in a subsequent study (3) that showed reductions in day and night BP and HR as well as an increase in stress-induced pressor responses.

There is much information on the effect of exogenous OT on cardiovascular parameters. Many studies use acute injection protocols with tail-cuff BP monitoring. Peripheral injection of OT produced both increases and decreases in BP (31, 33). The increase was short lived, whereas the depressor response lasted for hours or days. When injected directly into the brain stem, OT produced a marked increase in BP (>30 mmHg) (26). There are also numerous studies, which show a relationship between blood volume, pressor status, and OT secretion. Hypotension and hypovolemia activate OT neurons and increase peptide secretion (20, 21, 28, 39). Because OT is natriuretic, one might predict sodium retention and volume expansion in the peptide-deficient condition (17, 45). However, there are no long-term changes in vascular volume/osmolar status and no alterations in sodium balance (13). The OTKO +/− mice do show an enhanced sodium appetite, suggesting some subtle sensory or balance change. OT-deficient mice consume fivefold more salt solution under need-free conditions and sevenfold more following overnight fluid deprivation (1, 34). OT replacement produced a marked reduction in saline intake along with a reduction in salt excretion (13).

Table 2. Parameters of logistic function curve (sigmoid fitting) for baroreceptor testing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control +/+</th>
<th>OTKO −/−</th>
</tr>
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<tbody>
<tr>
<td>Average MAP, mmHg</td>
<td>117 ± 6</td>
<td>113 ± 5</td>
</tr>
<tr>
<td>Average HR, beats/min</td>
<td>577 ± 12</td>
<td>511 ± 17*</td>
</tr>
<tr>
<td>Logistic function curve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower plateau, beats/min</td>
<td>475 ± 20</td>
<td>460 ± 19</td>
</tr>
<tr>
<td>Upper plateau, beats/min</td>
<td>626 ± 24</td>
<td>663 ± 11</td>
</tr>
<tr>
<td>HR range, beats/min</td>
<td>151 ± 33</td>
<td>203 ± 22</td>
</tr>
<tr>
<td>MAP50, mmHg</td>
<td>127 ± 9</td>
<td>109 ± 5</td>
</tr>
<tr>
<td>Gain, beats-min−1-mmHg−1</td>
<td>−41 ± 1.2</td>
<td>−13.1 ± 2.5*</td>
</tr>
<tr>
<td>MAP range, mmHg</td>
<td>93 ± 12</td>
<td>40 ± 3*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 control +/+ mice and n = 9 OTKO −/− mice. MAP50, MAP at midrange; MAP range, interval of the x-axis between lower and upper plateaus. *P < 0.05 vs. control +/+ group.

Fig. 4. Individual sets of data points and fitted curve for baroreflex test in control +/+ (A) and OTKO −/− mice (B). Larger points represent average control values for MAP and HR.

Fig. 5. Group average logistic function curve showing the relationship between MAP and HR during baroreflex testing in control +/+ (n = 7) and OTKO −/− (n = 9) mice. Points represent the average control values of MAP and HR during loading/unloading of the baroreceptors. *P < 0.05, OTKO −/− vs. control +/+ mice.
A direct link between the OT system and hypotension cannot be established with surety. Certainly, OT's removal and the consequent lack of peptidergic signaling produce a cascade of changes. This could involve brainstem transmission and modulation of sympathetic and parasympathetic outflow. Afferent renal and brain pathways may also be altered in the knockout mice. OT antagonists attenuated the natriuresis following unilateral nephrectomy (19) and hypotension-induced renin, vasopressin, and HR responses (18). These results suggest that OT (besides its direct peripheral effects) is involved in the afferent signaling of the acute renal responses. The functional consequence resulting from the interaction between afferent × efferent OT effects on cardiovascular control remains to be determined.

Previous studies suggested a role for OT in the regulation of baroreflex function (16, 27, 32), an idea supported by our findings in the OTKO −/− model. There was a dramatic increase in the gain of the reflex (greater than 3-fold) as well as a decrease in the operating pressure range of the baroreflex function. There was a noticeable decrease in the bradycardia phase, suggesting that OT facilitates reflex reduction in HR. OT also appears to decrease the sensitivity of the reflex at the midpoint of the curve (around baseline values) and extends the pressure interval from maximal bradycardia to maximal tachycardia. Immunohistochemical staining and retrograde/antegrade tracing methods have shown dense oxytocinergic projections from hypothalamic centers to integrative cardiovascular areas in the brain stem (7, 26, 30, 38). Administration of both peptide and antagonist into discrete areas of the dorsal brain stem or spinal cord altered local neuronal activity (9, 11, 43). Injections of OT have divergent effects on reflex bradycardia, enhancement after intravenous injection, and a depression after intracisternal administration (32, 37). Our recent studies indicate that oxytocinergic projections from hypothalamus to NTS/DVC facilitate the slow down of the heart under various conditions (5, 16, 27). The present results confirm and extend this observation, showing that deletion of the OT gene and its peptide blunts the bradycardic but also facilitates the tachycardic response to depressor challenges. This may be partially explained by the set point for basal HR in OTKO −/− mice that is in the middle of the sympathetic range. This means that HR operates at a lower level, resulting in a higher sympathetic reserve to the heart. This reserve is noticeable when animals are tested with hypertensive challenges. The larger HR increase in the OTKO −/− group after parasympathetic blockade is likely the result of a downward displacement of basal HR relative to the maximal sympathetic response, rather than increased cholinergic drive. It should be stressed that the slightly high vagal tone at rest and the high intrinsic HR in the −/− group could also contribute to the downward displacement of baseline HR. Changes in tachycardic response were not observed in rats following OT receptor blockade restricted to the NTS/DCV (16), indicating a more generalized action of OT in the central adjustment of HR. The full anatomic map for central oxytocinergic control of cardiovascular function is not established; however, pieces of the puzzle indicate participation of the hypothalamic paraventricular nucleus (site of peptide biosynthesis) (8, 29), NTS/DVC brain stem integrative centers (5, 11, 16, 36), and the spinal cord (19, 41, 43).

The animals lacking OT show an increase in reflex gain over a smaller MAP interval. The assumption is that if OT's removal mediates this action directly, then central OT decreases gain while increasing the operational range of the reflex. Blunting of baroreceptor reflex control of HR has been described as a characteristic response of hypertensives with high sympathetic tone (4). However, both control and OTKO −/− mice exhibited a high sympathetic tone as demonstrated by the BP responses to β1-adrenergic and ganglionic blockade. Therefore, it appears that OT can modify reflex sensitivity, independent of the magnitude of sympathetic tone. Previous results showed that OT administration into the NTS/DVC modified reflex control of HR without changing the magnitude of sympathoexcitatory response to baroreceptor stimulation (16). In addition, our data indicate that OT is involved in setting the intrinsic HR, determining when present a low intrinsic value. Previous studies described OT-induced bradycardia as a central (5, 16) or peripheral effect (15, 33, 37). Although we have no information on a direct OT effect on intrinsic HR, this new observation is in accordance with the demonstration of OT receptor mRNA expression in the cardiac atria and ventricles (14) and the demonstration of OT synthesis in the heart, with the highest concentration found in the right atria (15).
In conclusion, this study presents the results of a comprehensive investigation of cardiovascular function in conscious mice lacking the OT gene. Differences were noted in basal BP, baroreflex function, and autonomic balance, supporting the idea that the OT secretory system is important in the regulation of cardiovascular function.

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